a. selecting Y and $D_h$ to correspond to each other such that is Y is greater than or equal to approximately $4.16D_h - 385$;

b. preparing a solution of polyvinyl alcohol having the parameters selected from step a.

c. subjecting said solution to a multiple-cycle freeze-thaw procedure,

which provides for a stable hydrogel and reduces or eliminates syneresis upon storage of the formulation for at least six months at a storage temperature in the range of approximately 5°C to 40°C.

## REMARKS

Claims 1-21, 23, 26-28, and 31-38 have been cancelled. Cancellation of these claims is without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicant expressly reserves the right to file one or more continuing applications hereof containing these cancelled claims.

Independent claim 22 has been amended to include language formerly found in claims 23, 26, 27, and 28. Claims 24 and 29 were amended to correct dependencies due to the cancellation of certain claims.

Currently pending are three independent claims 22 new independent claims 31 and 32 and dependent claims 24, 25, 29, and 30. A clean set of claims in included herewith as Exhibit A.

## A. LACK OF ANTECEDENT BASIS – CLAIMS 26 -27

On page 8 of the 19 October 1998 Office Action, the examiner asserts a lack of antecedent basis in claims 26 and 27 for failure to include an upper limit for the value of Y. Independent claim 22 has been amended to recite a range for Y of approximately 10 wt % to 30 wt % of the hydrogel. This range was taken from cancelled claims 26 and 27. As the upper limit of Y is now included in independent claim 22, this objection should be withdrawn.

## B. SECTION 112 ENABLEMENT REJECTION – CLAIMS 22-30

On page 8, in the last paragraph of the 19 October 1998 Office Action, the examiner asserts a lack of enablement for polymers other than those with the recited characteristics regarding viscosities, concentration and percent hydrolysis. Claim 22 has been amended to include ranges of parameters, supported by the specification, for the properties of average viscosity molecular weight, concentration, and percent hydrolysis. As these limitations are now included in all independent claims, Applicant respectfully requests that the enablement rejection be withdrawn.

## C. REJECTION UNDER 35 USC § 112, SECOND PARAGRAPH – CLAIMS 22-30

On page 9, in the first paragraph, of the 19 October 1998 Office Action, the examiner asserts that claims 22-30 are rejected because the language "..in a manner..", recited in claim 22, is vague and fails to particularly point out and distinctly claim the invention. Independent claim 22 has been amended to include two formulas, recited in the specification, which relate a value of the concentration of the polymer (Y) to the value of the percent hydrolysis ($D_h$) of the polymer.

As there is now contained in the single independent claim 22, a specific method of selecting the values of Y and $D_h$ Applicant respectfully requests that this rejection be withdrawn.

**D. ANTICIPATION BY KOBAYASHI PATENT – CLAIMS 22-30**

On the last paragraph of page 9 of the Office Action, the examiner asserts that all claims are anticipated based upon the Kobayashi patent, United States Patent No. 5,141,973. In order to function as an anticipating reference, each and every limitation in the proposed claim must be recited in the reference. There is nothing in Kobayashi which describes, discloses or even hints at a method for reducing syneresis by selecting the concentration of polyvinyl alcohol based upon the degree of hydrolysis of that polyvinyl alcohol in order to reduce or eliminate syneresis. Further, the Kobayashi patent addresses issues of fabricating a hydrogel to be used as a phantom for MRI imaging studies. There is no disclosure in Kobayashi about forming a hydrogel which contains a therapeutic amount of a drug to be used. Thus Applicant asserts that claims 22-30 are not anticipated by the Kobaysahi reference.

Independent Claim 22 has now been amended to contain further details regarding the relationship between the concentration of the polyvinyl alcohol (Y) and the degree of hydrolysis ($D_h$). Kobayashi contains no hint or suggestion of the claimed relationship between Y and $D_h$. Accordingly, Kobayashi cannot anticipate the amended claims and Applicant respectfully request that the rejection over Kobayashi be withdrawn.

## E. CONCLUSION

As all objections and rejections raised by examiner have been addressed by the amendments and remarks filed herewith, Applicant asserts that the application is in condition for allowance, issuance of which is earnestly solicited.

Respectfully submitted,

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**EXHIBIT A**

22. [AMENDED] A method for eliminating or reducing syneresis in a pharmaceutical hydrogel formulation comprised of (a) a therapeutically effective amount of a drug in (b) a hydrogel comprised of water and polyvinyl alcohol having an average viscosity molecular weight between approximately 10,000 and 400,000, wherein the polyvinyl alcohol has a predetermined degree of hydrolysis $D_h$ between approximately 95% and 99% and represents Y percent by weight in a range of approximately 10 wt. % to 30 wt % of the hydrogel, the method comprising

a. selecting Y and $D_h$ to correspond to each other such that if $D_h$ is greater than approximately 97.5% then Y is greater than or equal to approximately $5D_h - 479$ or if $D_h$ is less than approximately 97.5% then Y is greater than or equal to approximately $4.16D_h - 385$;

b. preparing a solution of polyvinyl alcohol having the parameters selected from step a; and

c. subjecting said solution to at least a single-cycle freeze-thaw procedure if Dh is greater than approximately 97.5% or subjecting said solution to a multi-cycle freeze-thaw procedure if Dh is less than approximately 97.5%

which provides for a stable hydrogel and reduces or eliminates syneresis upon storage of the formulation for at least six months at a storage temperature in the range of approximately 5°C to 40°C.

24. [Amended] The method of claim 22, wherein $D_h$ is in the range of approximately 96% to 99% and Y is in the range of approximately 12 wt. % to 25 wt %.

25. The method of claim 22, wherein syneresis is reduced or eliminated upon storage of the formulation for at least six months at a storage temperature in the range of approximately 20°C to 40°C.

29. [Amended] The method of claim 22 [28] wherein the polyvinyl alcohol has a viscosity average molecular weight in the range of approximately 12,000 to 200,000.

30. The method of claim 29, wherein the polyvinyl alcohol has a viscosity average molecular weight in the range of approximately 15,000 to 100,000.

31. A method for eliminating or reducing syneresis in a pharmaceutical hydrogel formulation comprised of (a) a therapeutically effective amount of a drug in (b) a hydrogel comprised of water and polyvinyl alcohol having an average viscosity molecular weight between approximately 10,000 and 400,000, wherein the polyvinyl alcohol has a predetermined degree of hydrolysis $D_h$ between approximately 95% and 99% and represents Y percent by weight in a range of approximately 10 wt. % to 30 wt % of the hydrogel, the method comprising

a. selecting Y and $D_h$ to correspond to each other such that $D_h$ is greater than approximately 97.5% and Y is greater than or equal to approximately $5D_h - 479$;

b. preparing a solution of polyvinyl alcohol having the parameters selected from step a; and

c. subjecting said solution to at least a single-cycle freeze-thaw procedure,

which provides for a stable hydrogel and reduces or eliminates syneresis upon storage of the formulation for at least six months at a storage temperature in the range of approximately 5°C to 40°C.

32. A method for eliminating or reducing syneresis in a pharmaceutical hydrogel formulation comprised of (a) a therapeutically effective amount of a drug in (b) a hydrogel comprised of water and polyvinyl alcohol having an average viscosity molecular weight between approximately 10,000 and 400,000, wherein the polyvinyl alcohol has a predetermined degree of hydrolysis $D_h$ between approximately 95% and 99% and represents Y percent by weight in a range of approximately 10 wt. % to 30 wt % of the hydrogel, the method comprising

a. selecting Y and $D_h$ to correspond to each other such that is Y is greater than or equal to approximately $4.16D_h - 385$;

b. preparing a solution of polyvinyl alcohol having the parameters selected from step a; and

c. subjecting said solution to a multiple-cycle freeze-thaw procedure,

which provides for a stable hydrogel and reduces or eliminates syneresis upon storage of the formulation for at least six months at a storage temperature in the range of approximately 5°C to 40°C.